REMARKS

Status of the Claims

Claims 1-5 are pending. Claims 6-19 are canceled. Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications.

No amendments are made. The listing of the claims is presented for the convenience of the Examiner. No new matter is entered.

Claims 1-3

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bernat et al. (U.S. Patent No. 5,989,578) or Uchiyama et al. (Stroke, vol. 20, no. 12, pp. 1643-1647) in view of Asai et al. (Annual Report of Sankyo Research Laboratories, 1999, vol. 51, no. 1-44).

Bernat and Uchiyama are cited by the Office Action as teaching a combination of either clopidogrel (Bernat) or ticlopidine (Uchiyama) with aspirin with a "synergistic" effect (OA, p. 3, lines 9-10). The Office Action argues that

> Bernat discloses 1 to 500 mg per clopidogrel or ticlopidogrel [sic] to 1 to 500 mg per aspirin (column 3, lines 21-28; column 4 lines 18-32; Tables; claims) and Uchiyama whereas Uchiyama discloses 300 mg per aspirin and 200 mg per ticlopidine ("Results" and "Discussion).

(OA, p. 3, lines 10-13). The Office Action relies on Asai as follows:

> Asai teaches that CS-747 (which is 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine) is effective as ADP receptor blocking antiplatelet agent without any serious adverse effects and more potent than ticlopidine or clopidogrel (see especially page 10-43).

(OA, p. 3, lines 14-17). The Office Action concludes that

> One having ordinary skill in the art would have motivated to select CS-747 (which is 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-

> fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine with the expectation that substitution of ticlopidogrel [sic] or clopidogrel with CS-747 would not significantly alter the analogous property of the compound of the reference having ADP receptor blocking antiplatelet agent while providing better safety and tolerability profile to the patient over ticlopidogrel [sic] or clopidogrel. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2131.01(a).

(OA, p. 4, lines 3-11). Essentially, the Office Action concludes that CS-747, when combined with aspirin, would provide "better safety and tolerability" than ticlopidine or clopidogrel while at the same time CS-747 would "not significantly alter the analogous property of the compound of the reference having ADP receptor blocking antiplatelet agent" (OA, p. 4, lines 3-11). With respect to the weight ratio as claimed, the Office Action concludes that "refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation" (OA, p. 4, lines 16-20).

In response to the previously-submitted arguments, the Office Action states that "Asai provides an ample motivation to arrive at the instant invention" (OA, p. 6, lines 13-14), and that the motivation to combine the references can be found in Asai's teaching, as summarized by the Office Action, that "CS-747 is more potent than ticlopidine or clopidogrel as ADP receptor blocking antiplatelet agent while providing better safety and tolerability profile to the patient" (OA, p. 6, line 22, through p. 7, line 4).

Applicants respectfully traverse for at least the reasons that the composition according to the claims meets a long-felt need for treatment and prevention of diseases caused by thrombus or embolus with greater predictability (i.e., with less interpatient variability), and that the claimed

invention provides unexpected results in providing less interpatient variability where the combination of aspirin and clopidogrel is known to exhibit high interpatient variability.

Long-Felt Need

Present methods of treatment with antiplatelet therapy can include the administration of both clopidogrel and aspirin for dual antiplatelet therapy (see PLAVIX® Prescribing Information, "Dosage and Administration," revised May 2009). The combination of clopidogrel and aspirin is favored over ticlopidine and aspirin for dual antiplatelet therapy because of FDA-required warnings that ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP) (see TICLID® Prescribing Information, revised March 2001).

However, there is an unmet need in antiplatelet therapy with clopidogrel and aspirin. Specifically, the combination of clopidogrel and aspirin yields considerable heterogeneity in the response by individual patients to the combination of drugs. For example, studies have estimated that adequate platelet effects are not achieved in 5% to 45% of patients taking aspirin and 4% to 30% of patients taking clopidogrel (see, for example, Lev et al., "Aspirin and Clopidogrel Drug Response in Patients Undergoing Percutaneous Coronary Intervention," Journal of the American College of Cardiology, 47(1):27-33 (2006)). Studies have also found that about 50% of patients who are aspirin resistant are also resistant to clopidogrel. See, for example, Lev, p. 29, right column: "Regardless of which aspirin resistance definition was used, about 50% of patients who were aspirin resistant were also resistant to clopidogrel."

The problem of inconsistent response (i.e., high interindividual variability in response) to aspirin, ticlopidine, and/or clopidogrel was recognized in the art at least as of August 2000. See,

for example, Van De Graaff et al., "Variable Interindividual Responses to Antiplatelet Therapies- Do They Exist, Can We Measure Them, and Are They Clinically Relevant?" Heart Drug, 1(1):35-43 (2001), available online August 2000. In referring to the thienopyridine class of compounds, Van de Graaff states "[a]lthough not as well studied as with aspirin, interindividual variability has also been observed in platelet reactivity during treatment with this class of medication," (Id., p. 39, left column, ll. 26-28). Van de Graaff also states

> Variable degrees of platelet blockade, based on in vitro assays of platelet function, have been consistently demonstrated in persons taking aspirin, thienopyridines and GP IIb/IIIa inhibitors.

(Id., p. 41, right column, ll. 30-34).

The problem of inconsistent response (i.e., high interindividual variability in response) is clinically relevant because studies have shown that dual drug-resistant patients have a more than two-fold increase in the rate of myonecrosis compared with drug-sensitive patients, as well as higher marker levels associated with higher risk of death, myocardial infarction, and repeat revascularization for patients following certain undergoing dual antiplatelet therapy. See, for example, Lev, p. 32, paragraph bridging left and right columns: "We evaluated the incidence of CK-MB elevation following PCT, which has been consistently shown to be associated with higher risk of death, MI, and repeat vascularization." In another study, aspirin-resistant patients had a 2.9-fold increased risk of CK-MB elevation compared with aspirin-sensitive patients, where CK-MB elevation is associated with a higher risk of death, among other poor clinical outcomes (see Chen et al., "Aspirin resistance is associated with a higher incidence of myonecrosis after nonurgent percutaneous coronary intervention despite clopidogrel pretreatment," J Am Coll Cardiol, 43:1122-6, 1125 (2004)). The clinical relevance of resistance was also appreciated at least as of August 2000, where Van de Graaff states that "[s]mall studies

have suggested the clinical importance of this resistance to therapy in aspirin-treated patients," (see Van de Graaff, p. 41, right column, ll. 34-35).

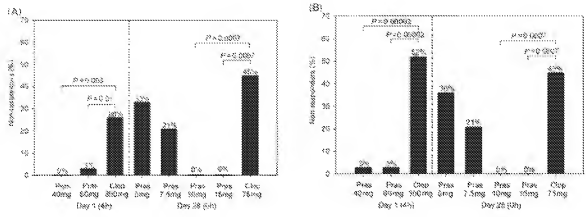
Because of significant populations of patients for whom prior combinations did not provide adequate therapy, the art recognized the need for new alternatives to treat patients exhibiting resistance to clopidogrel/aspirin. See, for example, Van de Graaff, which states that

> Importantly, clinical trials have not uniformly supported the rationale of using higher dosing of antiplatelet medication to overcome the effect of drug resistance [20-23]. These data suggest that alternative methods of platelet blockade must be sought for patients resistant to all doses of conventional antiplatelet medication.

(Van de Graaff, p. 41, right column, ll. 21-27). Since the problem of drug resistance is not overcome simply by increasing the dose of antiplatelet medication, the art was without any obvious solution to treat drug-resistant individuals.

Unexpected Results

The administration of prasugrel and aspirin surprisingly addresses and significantly reduces the problem of inconsistent response to dual antiplatelet therapy with clopidogrel and aspirin. See Jernberg et al., "Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease," European Heart Journal, 27: 1166-1173 (2006). Jernberg demonstrates that the administration of prasugrel and aspirin provides for a dramatic reduction in the percentage of non-responders. See, for example, Figures 4(A) and 4(B):



(Jernberg, p. 1170).

Figures 4(A) and 4(B) show the percentage of non-responders according to two analytic tests. In 4(A), non-responders were defined as subjects with IPA (inhibition of platelet aggregation) <25% in response to challenge with 5 micromolar ADP, which normally induces platelet aggregation. In 4(B), non-responders were defined as subjects with IPA <20% in response to challenge with 20 micromolar ADP.

All subjects in Figure 4 received 325 mg/day aspirin (see Jernberg, p. 1167, Study Design), combined with either prasugrel (initial loading dose of 40 or 60 mg, followed by daily maintenance doses of 5, 7.5, 10, or 15 mg) or clopidogrel (initial loading dose of 300 mg, followed by daily maintenance dose of 75 mg). The clopidogrel doses were based on the approved doses for loading and maintenance.

After administration of loading doses, only 0% or 3% of subjects with loading doses of 40 mg or 60 mg prasugrel in combination with aspirin were non-responders, while 26% or 52% of the clopidogrel/aspirin subjects were non-responders, depending on whether the challenge was 5 or 20 micromolar ADP. After administration of maintenance doses for 28 days, 0% of the subjects with 10 or 15 mg of prasugrel plus aspirin were non-responders, while 45% of the clopidogrel/aspirin subjects were non-responders.

This data provides important evidence that administering prasugrel and aspirin meets the long-felt need for a more consistent response in the treatment of non-responding patients with antiplatelet therapy. While the results of Jernberg were obtained through co-administration of separate aspirin and prasugrel tablets (see Jernberg, p. 1167, Study Design), administering a pharmaceutical composition comprising aspirin and prasugrel according to the present claims would yield the same effect as described in Jernberg.

Further evidence of the significance of the present invention is provided by the FDA's Cardiovascular and Renal Drugs Advisory Committee which evaluated data regarding antiplatelet therapy, including the data discussed above from Jernberg, at its February 3, 2009 meeting (see Presentation to the Cardiovascular and Renal Drugs Advisory Committee, February 3, 2009, Slide #26, available at <<http://www.fda.gov/AdvisoryCommittees/CommitteesMeeting Materials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm125999.htm>>). In voting to approve prasugrel, two of the Committee members (Dr. Emil Paganini and Dr. Richard Cannon) specifically referred to the responder/non-responder issue as providing a basis for their approval (see Transcript, page 365). Dr. Cannon states

> I do think there was a compelling need for a drug that had more predictable pharmacokinetics and pharmacodynamics than clopidogrel. I think the issue of clopidogrel resistance is real and it matters, and I think this drug is a major advance in that regard.

(Transcript, pages 365-366). It is important to note that the data from Jernberg which provides the support for the statements of Dr. Paganini and Dr. Cannon is from patients receiving both prasugrel and aspirin.

None of the publications relied on by the Examiner provide any basis for one skilled in the art to have an expectation that the combination of prasugrel and aspirin could address the problem of inconsistent or variable response. For example, Van De Graaff teaches that the

problem of interindividual variability is a class effect for the thienopyridines, stating that "interindividual variability has also been observed in platelet reactivity during treatment with this class of medication" (see Van de Graaff, at page 39, left column, last line).

The Examiner's rejection is based on the improper belief that increased potency provides a "better safety and tolerability profile to the patient," (see Office Action, p. 7, l. 2). Such a belief is not supported by basic pharmacologic principles. According to such principles,

> The location of its dose-effect curve along the dose axis is an expression of the potency of a drug.

(Goodman and Gilman, The Pharmacological Basis of Therapeutics, Fifth Edition, p. 25, 1975). However, the position of a dose-effect curve on the dose axis provides no information regarding the efficacy of the drug, or, in this case, its ability to be active in patients for whom other drugs in the same class are inactive. As further stated in Goodman and Gilman,

> Potency is a relatively unimportant characteristic of a drug since it makes little difference whether the effective dose of a drug is 1 μg or 100 mg, as long as the drug can be administered in appropriate dosage. *Potency* is not necessarily correlated with any other characteristic of a drug, and there is no justification for the view that the more potent of two drugs is clinically superior.

(Id., at 25, emphasis added). Van de Graaff recognizes this property, and states that "[i]mportantly, clinical trials have not uniformly supported the rationale of using higher dosing of antiplatelet medication to overcome the effect of drug resistance," (see Van de Graaff, p. 41, right column, ll. 21-24).

The above statements from Goodman and Gilman, a pharmacology textbook, are consistent with and support the surprising and unpredictable property provided by the present invention of being able to treat persons who otherwise did not obtain benefit from treatment with other combinations. Moreover, the teachings of Goodman and Gilman contradict the reasoning of the Office Action. In other words, the literature suggests that the enhanced potency of

prasugrel itself is not predictive of the ability of the combination of prasugrel and aspirin to treat resistant individuals.

It is an unexpected result that the combination of prasugrel and aspirin not only address the problem of responders/non-responders in the first place, but also address the problem so completely. The data provided by Jernberg show that where almost half of the clopidogrel/aspirin subjects in the study were non-responders after 28 days of treatment with the approved maintenance dose, essentially all of the prasugrel/aspirin subjects could be shown to respond to treatment.

Accordingly, for at least the reasons that the claimed invention unexpectedly meets a long-felt need because it exhibits unexpected results, Applicants submit that none of the cited references, whether taken alone or in combination, render the claimed invention unpatentable. Having distinguished independent claim 1 from the art of record, Applicants submit that dependent claims 2 and 3 are patentable for at least the same reasons. However, Applicants reserve the right to separately address the patentability of those claims in the future should that become necessary.

Claims 4-5

Claims 4-5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bernat et al. (U.S. Patent No. 5,989,578) or Uchiyama et al. (Stroke, vol. 20, no. 12, pp. 1643-1647) in view of Asai et al. (Annual Report of Sankyo Research Laboratories, 1999, vol. 51, no. 1-44), and further in view of Koike et al. (U.S. Patent No. 5,288,726).

The Office Action relies on Bernat, Uchiyama, and Asai as discussed in the rejection of claims 1-3. The Office Action concedes that none of the three references teach specific

hydrochloride or maleate salt forms, however, the Office Action relies on Koike as teaching "compounds represented by formula (I) including 2-acetoxy-5-(alpha-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, wherein said compounds are prepared in pharmaceutically salts thereof including maleate and hydrochloride" (OA, p. 5, lines 6-10). The Office Action concludes that one would "select the claimed compounds in maleate or hydrochloride salt with reasonable expectation of success that preparation of said composition in maleate and hydrochloride salt form would not significantly alter the analogous properties of compound of the reference due to close structural similarity of the compounds" (OA, p. 5, lines 11-15).

Applicants respectfully traverse for at least the reasons that the composition according to the claims meets a long-felt need for a treatment of acute coronary syndrome with greater predictability (i.e., with less interpatient variability), and that the claimed compositions provide unexpected results in providing less interpatient variability where the combination of aspirin and clopidogrel is known to exhibit high interpatient variability.

Accordingly, for at least the reasons provided above, Applicants submit that none of the cited references, whether taken alone or in combination, render the claimed invention unpatentable. Having distinguished independent claim 1 from the art of record, Applicants submit that dependent claims 4 and 5 are patentable for at least the same reasons. However, Applicants reserve the right to separately address the patentability of claims 4 and 5 in the future should that become necessary.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request withdrawal of all rejections and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees which may be required for consideration of this paper to Deposit Account No. **50-3732**, Order No. 13509.105003US. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13509.105003US.

Respectfully submitted,
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